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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,291	06/10/2005	Kazufumi Yazaki	Q88235	9414

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EXAMINER
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MEAH, MOHAMMAD Y

ART UNIT	PAPER NUMBER
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1652

MAIL DATE	DELIVERY MODE
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07/27/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

Application No.

10/538,291

Applicant(s)

YAZAKI ET AL.

Examiner

Mohammad Meah

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 30 April 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-4 and 6-19 is/are pending in the application.
- 4a) Of the above claim(s) 1-3 and 17-19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 4, 6-16 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Claims 1-4, 5-19 are pending. Claims 4-16 were examined in the previous action.

Claims 1-3 and 17-19 remain withdrawn. With supplemental amendment of this application, the applicant, on dates on 4/30/07, cancelled claim 5 and amended claims 4, 6-15. Therefore claims 4, 6-16 will be examined.

### ***Claim objections***

Claims 14 and 16 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

### ***Claim Rejections***

#### ***USC 112 rejection 2<sup>nd</sup> paragraph***

Rejection of claims 4-13 under USC 112 rejection 2<sup>nd</sup> paragraph requirement is withdrawn after amendment of the claims. However claim 15 is remained rejected as indefinite in recitation " *Escherichia coli* selection strain is derived from *Escherichia coli* SD840 strain" because a strain can not be both strain SD840 and a derivative of SD840.

#### ***USC 112 rejection 1<sup>st</sup> paragraph written description***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

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terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 6-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of *E. coli* strain having expression of any exogenous gene or a genus of *E. coli* strain having expression of phenylalanine ammonia lyase selected using stress response index by measuring hydrogen peroxide decomposition. The *E. coli* strain claimed in the instant claims, having expression of any exogenous gene or a genus of *E. coli* strain having expression of phenylalanine ammonia lyase selected using stress response index by any means, is a large variable genus *E. coli* strains expressing many exogenous proteins. The specification teaches a few *E. coli* strains having expression of an exogenous gene encoding a phenylalanine ammonia lyase selected using stress response index (*E. coli* SD840 page 12 of the specification), which does not represent all strains recited in the instant claims. The specification neither teaches the structures of all genes nor teaches how all *E. coli* strains will be modified. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning

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compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at [www.uspto.gov](http://www.uspto.gov).

Applicants argument against 112 written description rejection, described on their amendment pages 1-2, is considered but not found persuasive because although a few *E. coli* strains having expression of an exogenous gene encoding a phenylalanine ammonia lyase selected using stress response index (*E. coli* SD840 page 12) are disclosed, these claims encompass selection of many *E. coli* strains having expression of an exogenous gene. The genus of *E. coli* strains recited in the claim is a large variable genus that applicant do not teach how all these diverse strain will be modified to have recited function. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 4, 6-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *E. coli* strain (SD840) does not reasonably provide enablement for any *E. coli* strain having expression of any exogenous gene or a genus of *E. coli* strain having expression of phenylalanine ammonia lyase selected using stress response index measured by measuring hydrogen peroxide decomposition. The claims broadly recite expression of any *E. coli* strain using any exogenous gene or a genus of *E. coli* strain having expression of phenylalanine ammonia lyase

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selected using stress response index. The specification fails to describe how any *E. coli* strain is modified to express any exogenous gene or any phenylalanine ammonia lyase gene.

Claims 4, 6-13 are so broad as to include many strains of *E. coli* having expression of any exogenous gene or any phenylalanine ammonia lyase selected using stress response index by any means. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number *E. coli* strains expressed with any gene. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a few genes such as specific phenylalanine ammonia lyases.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable(e.g., see Ngo et al. in the protein folding problem and tertiary structure

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prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MAS, pp 433 and 492-495). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Furthermore, there are many means of controlling gene function such as mutations of the gene itself, addition of inhibitors, modification of endogenous modulators, mutating individual nucleic acid, etc. It is not routine in the art to control a gene by any means to obtain desired outcome. Without knowing the structural feature of the protein it encodes, controlling the gene by any means (i.e., such as modification of the gene by mutations) to obtain desired function is unpredictable (e.g., see Ngo et al. in the protein folding problem and tertiary structure prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MAS, pp 433 and 492-495). Enough guidance is not given to enable the skilled artisan to express any *E coli* strain with a large number of genes and select highly expressed strains using stress response. The specification does not support the broad scope of the claims which encompass any *E. coli* strain expressed by any gene and how *E coli* strains' stress response regulated by any means with any gene encoding any protein because the specification does not establish: (A) regions of the DNA structure of a gene which should be modified to control expression and/or to regulate any *E. coli* strain's stress response (B) the general tolerance of *E. coli* stress response and expression in the modification of gene and extent of such tolerance towards the expression of the gene; (C) a rational and predictable scheme for modifying any gene residues with an expectation of obtaining the desired biological function; and / or controlling the gene by any means towards such biological function (D) the

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specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any *E. coli* strain having expression of any exogenous gene selected using stress response index. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, selecting any *E. coli* strain expressed with any exogenous gene is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants argument against 112 enablement rejection, described on their amendment pages 2-3, is considered but not found persuasive because although specification is **enabled** for a few *E. coli* strains (*E. coli* SD840 of page 12 of the specification) does not reasonably provide enablement for any *E. coli* strain having expression of any exogenous gene or a genus of *E. coli* strain having expression of phenylalanine ammonia lyase selected using stress response index measured by measuring hydrogen peroxide decomposition as discussed previously.

Applicants argue that the rejection under 35 U.S.C. §112, first paragraph is not proper because applicant is selecting *E. coli* strains by measuring hydrogen peroxide decomposition and the invention has nothing to do with gene expression. These are not persuasive because these claims encompass *E. coli* strains having expression of an



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exogenous gene, not method of finding stress response by measuring hydrogen peroxide decomposition. In fact applicant clone E-coli strain by gene manipulation (claims 15-16) which is contrary to applicants arguments. Finding stress responses by measuring hydrogen peroxide decomposition of known strain are well known to the skilled artisan but finding which strain from enormous variants of strains as claimed by applicants (expressing any exogenous gene) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the enormous numbers of DNAs are expressed in such e-coli strains. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

***CLAIM Rejection - 35 U.S.C 102******35 U.S.C 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Rejection of claim 4 under 35 U.S.C. 102(b) as being anticipated by Hitagawa et al. ( JP 08-140671) is withdrawn after applicants amendment of the claim.

***CLAIM Rejection - 35 U.S.C 103a***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Lockwood et al (WO94/19472) reference is withdrawn because applicant amend the claims ( from highly expressing *E. coli* to expressing *E. coli*)

Claims 4-15 are rejected under 35 U.S.C. 103(a) Rowbury et al. ( J. appld. Microbiol. 2001, 90, 677-695) in view of Seaver et al. ( J. Bacterol. 2001. pp 7182-7189).

Claims 4-8 are directed to *E. coli*. strain expressing any exogenous gene encoding any protein and Claims 9-15 are directed to *E. coli*. strain expressing any exogenous gene encoding any protein having PAL activity, wherein said strain is selected by measuring hydrogen decomposition as a stress response factor.

Rowbury et al. ( J. appld Microbiol 2001, 90, 677-695) teach that in cells of microorganisms, such as *E. coli* the stress response increases upon expression of exogenous genes (a foreign biological component including antibiotics, bacteriophages etc, page 678 and Table 1). Rowbury et al. also teach that such stress can be correlated with hydrogen peroxide build-up inside the cell ( page 692 last paragraph).

Seaver et al. teach measurement of hydrogen peroxide decomposition activity in growing *E. coli* strain. Seaver also teach that hydrogen peroxide forms in *E. coli* strain when said strain shows stress. It is easier to monitor stress response in *E. coli* by measuring the hydrogen peroxide decomposition.

Therefore a person of ordinary skill in the art is **motivated** to use Seaver's method of measuring hydrogen peroxide decomposition activity to select stress

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response *E. coli* strain wherein increase of exogenous gene is correlated with increase in stress response of said *E. coli* strain as taught by Rowbury et al.

As such it would have been obvious to one of ordinary skill in the art to express an *E. coli* strain with an exogenous gene and use the Seaver's method of measuring hydrogen peroxide decomposition activity to select *E. coli* strain based on stress response. Therefore claims 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowbury et al. ( J. appld. Microbiol. 2001, 90, 677-695) in view of Seaver et al. ( J. Bacterol. 2001. pp 7182-7189).

Applicants argument against Rowbury et al. for not teaching stress response in *E. coli* strain is not found persuasive. In fact whole review article is on stressed *E. coli* strain. Rowbury et al. teach that in *E. coli* the stress response increases upon introducing a foreign biological component (including antibiotics, bacteriophages etc, page 678 and Table 1) an exogenous gene is a foreign biological or chemicals to *E. coli*). Applicants argument that Seaver et al. ( J. Bacterol. 2001. pp 7182-7189) do not teach measurement of hydrogen peroxide decomposition activity in growing *E. coli* as a means of stress response factor is not found to be true as Seaver et al. in the Discussion section of the article ( page 7187 ) discussed quantification of hydrogen peroxide decomposition as a means of stress in growing *E. coli*.

**THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you

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have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

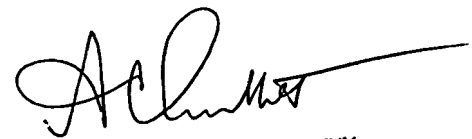
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Examiner, Art Unit 1652

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